# 24.10 Specific conditions affecting the central ne

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24.10 Specific conditions affecting
the central nervous system CONTENTS 24.10.1 Stroke: Cerebrovascular disease 6010 J. van Gijn (revised by Peter M. Rothwell) 24.10.2 Demyelinating disorders of the central
nervous system 6026 Alasdair Coles and Siddharthan Chandran 24.10.3 Traumatic brain injury 6042 Tim Lawrence and Laurence Watkins 24.10.4 Intracranial tumours 6048 Jeremy Rees 24.10.5 Idiopathic intracranial hypertension 6054 Alexandra Sinclair 24.10.1 Stroke: Cerebrovascular disease J. van Gijn (revised by Peter M. Rothwell) ESSENTIALS Cerebrovascular diseases include many pathological conditions but the principal categories are (1)  infarction—through occlusion of major arteries, small arteries or venous sinuses; and (2) haemor- rhage—most often through rupture of small arteries, arterial aneur- ysms, or capillaries. Epidemiology Strokes are common, with annual incidence rates for subjects aged over 55 ranging from 420 to over 1000 per 100 000. They are the most important case of disability in developed Western nations and the second most frequent cause of death after coronary heart dis- ease. About 80% of strokes are caused by cerebral infarcts, with the remainder due to haemorrhage, with 20% of these attributable to a

bleeding cerebral aneurysm. The annual incidence of transient is- chaemic attacks is about 50–100 per 100 000. General considerations Strokes typically present with a sudden onset of focal neurological deficit. Urgent imaging with CT or MRI allows rapid differentiation between haemorrhagic and ischaemic causes—with critical benefit for the introduction of appropriate treatment—and serial imaging may reveal the development of important complications such as rebleeding, ischaemia, or hydrocephalus that mandate specific interventions. The consequences of stroke are often devastating: sudden loss of a large amount of brain tissue affects much more than specific, local- ized functions such as movement, sensation, vision, and language. Mood, initiative, sense of humour, and speed of thought are among the essential aspects of mental life that can be severely affected. Management of patients with stroke requires their complex needs to be comprehensively addressed. The introduction of specialized clinical units for the multidisciplinary care of patients with stroke has been shown to improve clinical diagnosis and recovery, reducing the risk of death or institutionalized care by 14%. The introduction of urgent stroke prevention services for transient ischaemic attacks and minor stroke has reduced the risk of early recurrent stroke by about 80%. Pathophysiology of arterial occlusive disease Atherothrombosis is the main cause of occlusion of major arteries in the brain, typically by embolism from a source in the carotid artery, aorta, or heart. Whether occlusion of an artery supplying brain tissue actually leads to ischaemia depends on collateral pathways, which may be by (1) the circle of Willis, (2) connections between extracra- nial and intracranial vessels, (3) leptomeningeal anastomoses. Arterial occlusive disease—transient ischaemic attacks These, by definition, are due to ischaemia of a part of the brain, pro- ducing symptoms/signs that last for less than 24 h (usually for min- utes). The main presentations are with transient (1) hemiparesis, (2) dysphasia, (3) monocular visual loss, or (4) hemianopia. Without treatment (see ‘Secondary prevention’), the risk of stroke after a transient ischaemic attack is up to 20% in the first year and 7% in subsequent years.

24.10.1 Stroke: Cerebrovascular disease 6011 Arterial occlusive disease—cerebral infarction Classification—this has been attempted on the basis of time course (‘progressive’, ‘completed’), anatomy (which artery?), cause (e.g. large artery atherosclerosis, cardioembolism), or functional deficit (e.g. modified Rankin scale). The Oxfordshire Community Stroke Project system provides a useful and widely accepted compromise, defining four types of cerebral infarction: (1) total anterior circulation infarcts—with both cortical and subcortical involvement; (2) partial anterior circulation infarcts—more restricted and predominantly cor- tical infarcts; (3) posterior circulation infarcts—clearly associated with the vertebrobasilar arterial territory; (4) lacunar infarcts, confined to the territory of the deep perforating arteries. Specific treatments—several medical interventions aim at dissolving (thrombolysis and antithrombotics) or extracting (thrombectomy) the occluding clot, or at least preventing it from growing. Those of widest application are: (1) Thrombolysis—treatment of highly selected patients within 4.5 h of the stroke event (and the sooner the better) with intravenous recombinant tissue plasminogen ac- tivator (r-tPA) will avoid death or dependence in 55 patients per 1000 treated. (2) Thrombectomy is more effective than thrombolysis alone in selected patients with documented large artery occlusion. (3) Antiplatelet agents—treatment with aspirin, started within 48 h of onset, will avoid death or dependence in 13 patients per 1000 treated. Other interventions that are occasionally required include hemicraniectomy, which is effective in reducing mortality in patients with malignant hemispheric infarction and posterior decompression in patients with large cerebellar infarcts or haematoma. Secondary prevention—aside from control of lifestyle factors (ces- sation of smoking, reducing overweight, daily exercise), specific measures to reduce the risk of threatened stroke include

(1) Carotid endarterectomy—substantially decreases the risk of stroke in pa- tients with severe, symptomatic carotid stenosis. (2) Antiplatelet drugs—aspirin produces relative risk reduction of 13% in long-term risk of stroke, with addition of dipyridamole providing some further benefit, but the benefits of antiplatelet treatment in the acute phase are much greater; clopidogrel should be added to aspirin in the acute phase and may be continued as alternative long-term monotherapy. (3) Anticoagulants—with embolic sources in the heart, mostly from atrial fibrillation, coumadin anticoagulants (INR 2.5–4) remain a choice in the absence of contraindications, although new oral anti- coagulants appear to be at least as effective and safer. (4) Statins—re- duce the risk of stroke by about 20% per mmol/litre reduction in low-density lipoprotein cholesterol. (5) Antihypertensive drugs—the level of blood pressure is by far the most powerful risk factor for stroke; in individuals with a history of stroke or transient ischaemic attack, a blood-pressure-lowering regimen reduces the risk of stroke by 25 to 50% depending on the degree of blood pressure lowering, regardless of whether or not the blood pressure at baseline was con- sidered too high. Venous occlusive disease Aetiology—cerebral venous thrombosis often occurs in the context of a combination of predisposing factors (e.g. the oral contraceptive pill, pregnancy, or post-partum), in combination with some inherited disorder of coagulation such as the factor V Leiden mutation. Clinical features, investigation, and treatment—manifestations include headache, focal deficits, seizures, and impairment of consciousness. Imaging with CT/MRI reveals ‘venous’ infarcts that do not correspond to a known arterial territory and evidence of the underlying sinus thrombosis. Most physicians treat with anticoagu- lants, but evidence for their efficacy is not strong. Mortality is 5–30%. Primary intracerebral haemorrhage Aetiology—primary intracerebral haemorrhage usually occurs in the context of a combination of (1) anatomical factors—cerebral vas- cular lesions or malformations (e.g. arteriovenous or cavernous malformations, ruptured perforating arteries, amyloid angiopathy); (2) haemodynamic factors—most notably blood pressure, which is the most important treatable risk factor; and (3) haemostatic fac- tors—relating to platelet function or the coagulation system (e.g. oral anticoagulants). Clinical features, investigation, and treatment—in most cases history and examination provide few clues to the cause of an intracerebral haemorrhage, other than hypertension, but specific enquiry should always be made about use of oral anticoagulants and the pos- sibility of malignant disease (with bleeding into a metastasis), and evidence of a generalized haemostatic disorder should be sought. Brain imaging (CT or MRI) is the most important single investigation in patients with suspected intracerebral bleeding. There is no specific treatment for most patients, but therapeutic anticoagulation should be reversed, and surgical evacuation of large cerebellar haematomas should be considered. Subarachnoid haemorrhage Aetiology—ruptured aneurysms cause 85% of nontraumatic sub- arachnoid haemorrhages. Clinical features and investigation—presentation is with sudden, severe, and unaccustomed headache, with loss of consciousness at onset in 50%. Imaging with CT is the most important investiga- tion: scanning within three days reveals extravasation of blood in the basal cisterns in 95% of cases. Lumbar puncture is indicated if the history is convincing, but the CT scan is negative: xanthochromia of the supernatant after centrifugation of the cerebrospinal fluid sample is the most reliable diagnostic finding. CT and MR angiography are the methods of choice for demonstrating or excluding an aneurysm as the source of haemorrhage. Treatment—aside from general nursing and supportive measures, key issues are (1) prevention of rebleeding—without intervention, the risk of this is 30% in the month after presentation, with immediate mortality of 50%. Endovascular treatment (‘coiling’) is the preferred method to occlude the aneurysm and prevent rebleeding, but not all aneurysms can be treated in this way and operative clipping is still necessary for these patients. (2) Delayed cerebral ischaemia—occurs in up to 25% of patients with

a ruptured aneurysm, most commonly 5–14 days after the initial bleed. Nimodipine reduces the frequency of cerebral ischaemia and poor outcome by about one-third. Introduction History Intracerebral haemorrhage was first recorded by the Swiss phys- ician Wepfer (1620–95) and in more detail by Morgagni (1682– 1771) in Padua. Nonhaemorrhagic stroke, ‘serous apoplexy’,

section 24 Neurological disorders 6012 greatly puzzled the medical community until cerebral softening (‘ramollissement’) was recognized as a pathological entity in 1820 by Rostan (1790–1866), in Paris. Initially it was regarded as an inflammatory condition. The relationship of brain softening with arterial occlusion and atherosclerosis gradually dawned on the pathologists; it was firmly established by Rokitansky (1804– 78) in Vienna and Virchow (1821–1902) in Berlin. The term ‘in- farction’ was coined by Cohnheim, one of Virchow’s disciples. Subarachnoid haemorrhages and their usual source, intracranial aneurysms, were first recognized at the start of the 19th century; the diagnosis could (sometimes) be made during life from the start of the 20th century. In 1931 the Edinburgh neurosurgeon Norman Dott (1897–1973) carried out the first intracranial operation for a ruptured aneurysm, by wrapping it in muscle. Understanding cerebrovascular disease received great impetus with the advent of CT in the 1970s. Before that time, observations de- pended on post-mortem studies and on indirect neuroradiological studies such as angiography and pneumoencephalography. CT al- lowed rapid and reliable distinction between haemorrhagic and ischaemic stroke during life. Subsequently, CT and the newer tech- nique of MRI identified several subtypes of stroke, each requiring specific therapeutic measures. The rapid increase in diagnostic ac- curacy coincided with the emergence of the randomized clinical trial, which added considerably to pathophysiological reasoning as a basis for many medical interventions. Epidemiology of stroke Worldwide, stroke is the second most common cause of death after coronary heart disease, although it is the most important single cause of adult disability in the Western world. Stroke incidence is not technically difficult to measure but requires a great deal of time and resources. The few reliable studies, mostly from industrial coun- tries, show that age- and sex-standardized annual incidence rates for individuals aged 55 or more are between 420 and over 1000 per 100 000, depending on geographical region. More than half of strokes occur in people aged over 75 years. In Western Europe the overall age-adjusted incidence rates are falling, but the absolute number of strokes occurring remains approximately the same be- cause of the ageing population. The pathological type varies, even between studies with a high rate of CT, but a general estimate is that out of every five strokes four are infarcts and one a haemorrhage, and that one out the five haemorrhages is from a ruptured aneurysm (subarachnoid haemorrhage). The incidence of transient ischaemic attacks (TIAs) is about 50–100 per 100 000, but many more patients with a possible TIA are seen in clinical practice. In terms of an average general practice of 2400 people in Western Europe (1000 aged >55 years), four patients will have a stroke per annum, versus one having a TIA. Intracerebral haemorrhage will occur about twice every 3 years, and subarachnoid haemorrhage once every 8 years. Arterial occlusive disease The cerebral circulation and its disorders Brain tissue is critically dependent on a constant supply of oxygen and glucose. The cerebral blood flow (c.800 ml/min) accounts for 15–20% of the entire cardiac output, whereas the brain (c.1350 g) accounts for only 2% of the normal adult body weight. Neurons in the brain require a constant supply of adeno- sine triphosphate to maintain concentration gradients of ions across their membranes, necessary for the generation of action potentials. The resting brain consumes energy at the same rate as a 20-W light bulb. Whether occlusion of an artery in the brain or in the neck actually leads to ischaemia depends on collateral pathways. If an end-artery is occluded and there is no collateral circulation at all, ischaemic symptoms will occur within seconds.

Neurons will start dying within minutes and within hours the entire supply area of the artery will be irreversibly damaged. In contrast, permanent occlusion of a major artery (e.g. the internal carotid artery) may be asymptomatic in the presence of adequate collateral circulation. Broadly speaking, three levels of collateral circulation can be distinguished (Fig. 24.10.1.1; these can be thought of as three lines of defence): 1 The circle of Willis (Fig. 24.10.1.2)—even if no blood at all is flowing to the brain from one or even both internal carotid ar- teries, collateral flow from the other internal carotid artery or the basilar artery, via an intact circle of Willis, may ensure an ad- equate blood supply in the territory of the occluded artery. 2 Connections between extracranial and intracranial vessels—if the internal carotid artery is occluded at its origin, collateral channels may develop via the external carotid artery. Branches supplying the outer orbit may connect with branches to the retina, resulting in a reversed flow in the ophthalmic artery. From there, blood reaches the distal part of the internal carotid artery. Similarly, branches of the occipital arteries (normally supplying the neck muscles) may fill the basilar artery if this is occluded at its origin. 3 Leptomeningeal anastomoses—if, for example, the main stem of the middle cerebral artery is occluded, its terminal branches at the surface of the brain may anastomose with similar branches of Posterior cerebral artery Vertebral artery Ophthalmic artery Basilar artery Junction of vertebral arteries Common carotid Internal carotid External carotid Posterior communicating artery Fig. 24.10.1.1 Arterial supply of the brain. The drawing shows, on the right side, the internal carotid artery, external carotid artery, and vertebral artery. If a main artery is occluded, then collateral flow may occur via the circle of Willis (see also Fig. 24.10.1.2).

 the anterior and posterior cerebral arteries; in this way the cere- bral cortex in the territory of the occluded artery is spared, partly or wholly, although the deep territory will still be ischaemic. Atherothrombosis is the major cause of occlusion of major arteries in the brain or the neck. Two important qualifications should be made. First, atherosclerosis of intracranial arteries is relatively un- common, at least in white people at younger ages (vs. black or East Asian people). This means that, in the Western world, brain infarc- tion is usually caused by embolism, in which thrombus has been dislodged from an upstream lesion. The source can be the carotid ar- tery, aorta, or heart. Second, atherosclerosis is not a sufficient cause in itself: not every person with severe atherosclerotic disease has an ischaemic stroke. Other relevant factors are collateral circulation, ir- regularity of the plaque, blood turbulence, platelet aggregation, and the balance of clotting factors. Diagnosis of transient ischaemic attacks (TIAs) TIAs are important to diagnose because they are potential harbin- gers of stroke. They precede cerebral infarction probably in about 25% of cases. The term ‘transient ischaemic attack’ is rather imprecise, because it tacitly implies three restrictions. To begin with, it refers only to the brain and not to angina pectoris or intermittent claudication. Also excluded is transient ischaemia of the entire brain, such as occurs in syncope or ventricular fibrillation. In medical usage, only ischaemia of a part of the brain corresponds with the term TIA. Finally, how transient is transient? Traditionally the limit for the duration of symptoms has been set at 24 h. Obviously, this threshold has more to do with astronomy than with biology or disease. In fact, most TIAs last minutes, not hours. The longer an attack lasts, the greater the chance that CT or MRI afterwards will show a relevant ischaemic lesion. In terms of patient management, the essential question is not whether the attack has lasted 3 minutes, 3 days, or 3 weeks, but what its cause is and how recurrences can be prevented. Moreover, in recent years, diffusion-weighted MRI scanning has shown that about 30% of patients with TIA have small high-signal lesions on brain imaging that usually correspond clinically with the symptoms of the event and appear to represent areas of acute cerebral infarc-

tion. Acute diffusion-weighted imaging (DWI) changes increase in frequency as the duration of symptoms increases and are associated with a higher early risk of major stroke. What actually happens in the brain during a given period of is- chaemia can often only be guessed at. The usual assumption is that an embolus, most often consisting of platelets or loosely organized thrombus, temporarily blocks an intracerebral vessel and then dis- solves into smaller fragments. There is scant evidence for this phe- nomenon, apart from chance observations during fundoscopy, angiography, or surgery. Other explanations, applicable only to a minority, include marginal flow, secondary to severe narrowing or occlusion of arteries. The role of hypertension is also uncertain, but many patients with TIA have high blood pressure in the acute phase, which might be important in influencing susceptibility to cerebral ischaemia in the presence of embolization. The diagnosis of a TIA is problematic. That one has to rely on the history alone is a first difficulty (it requires time, skill, and patience). A greater source of error is that the term TIA is an interpretation ra- ther than a description. Main varieties of transient ischaemic attacks There are four kinds of symptoms that can safely be regarded as TIAs, given that the onset is sudden (within seconds), all symptoms appear at the same time, without ‘march’, and there is no better explanation. Transient weakness of one-half of the body Apart from weakness, there may also have been numbness. Isolated numbness or pins and needles on one side of the body are a less common manifestation of transient cerebral ischaemia; other causes such as overbreathing or focal seizures should also be considered. Weakness and numbness are closely related perceptions, and one should not take these or other expressions (‘an arm gone dead’) for granted. It is important to make sure that the problem had to do with moving the limbs or the face on one side (facial weakness on one side often manifests itself through slurred speech or drooling), and not with what it felt like when those body parts were touched or with spontaneous sensations. It is also important to verify whether the problem was in two of three body areas, and that it was not just a leg or arm gone to sleep after a nap in older people. Transient loss of the ability to find words or to understand them The medical term for this type of TIA is dysphasia or aphasia; in this case patients and relatives may not recognize the episode as representing a problem of language but will often describe the at- tack as ‘confusion’. It is helpful to ask specific questions about the ability to put thoughts into words (motor dysphasia), and about having been able to understand what was said (sensory dysphasia). If a patient can write sentences but cannot speak, the cause is almost certainly psychological.
A frequent problem is the distinction be- tween dysphasia (disorder of language) and dysarthria (disorder of Anterior communicating artery Basilar artery Posterior communicating artery Internal carotid artery Middle cerebral artery Anterior cerebral artery Posterior cerebral artery Posterior inferior cerebrellar artery Vertebral artery Fig. 24.10.1.2 The arterial circle of Willis, at the base of the brain.

section 24 Neurological disorders 6014 articulation). To ask whether pronunciation was difficult may not be very helpful. After all, in both cases the patient’s thoughts are clear and the distinction between the right words and the right sounds is rather academic. A more useful question is whether the words made sense and whether they were in the right order. Dysphasia implies a lesion of the left hemisphere in right-handed people, and in 30% of strong left-handers. Transient loss of vision in one eye The difficulty in this case is to distinguish transient monocular blindness from loss of vision on one side in both eyes (hemianopia). Either type of attack can be interpreted by the patient as a problem in one eye. The distinction has practical implications, as monocular attacks of blindness should lead to investigation of the ipsilateral internal carotid artery in the neck with a view to angiography and surgery, whereas isolated hemianopia mostly (in 80%) reflects a

dis- order in the vertebrobasilar circulation, in which case treatment will often be medical. The key question to ask is whether patients have alternately covered each eye during the attack.
A surprisingly large proportion of patients have done so, but they will not always offer this information without prompting. On having covered the ‘good eye’ in case of hemianopia, the patient should still have been able to see with the ‘bad eye’, although only the nasal half of the visual field. With a monocular disorder the blindness should have been com- plete after covering the unaffected eye. In practice, however, the dis- tinction between hemianopia and monocular visual loss can still be difficult, particularly if the hemianopia was macular-sparing, such that central vision (i.e. faces or written text) was preserved. Transient loss of vision in one hemifield Hemianopia reflects dysfunction of the occipital lobe. It is also a common aura in migraine attacks; these auras may occur without ensuing headache, especially in older people. It is, therefore, im- portant for the physician to enquire about the mode of onset: flashing lights, bright colours, zigzag lines, and a gradually expanding deficit all argue in favour of a migrainous attack, rather than ischaemia in its restricted sense of a stroke warning. Differential diagnosis of TIAs Box 24.10.1.1 lists types of attacks that should in general not be regarded as TIAs, either because of positive phenomena, such as rhythmic jerking, that are rarely due to focal ischaemia, or because other causes are much more likely. In particular, the tendency to label any episode of ‘dizziness’ in older people as ‘vertebrobasilar ischaemia’ or, even worse, ‘vertebrobasilar insufficiency’ should be resisted unless there is compelling evidence of severe disease of the vertebral or basilar arteries. The other isolated neurological symp- toms listed in the box can sometimes be due to TIAs, but there is less diagnostic certainty and these events are sometimes referred to as transient neurological attacks (TNAs). Recent research shows that the risk of major stroke after a TNA is relatively low, but that they are associated with a relatively high long-term risk of vascular events. In addition, some specific disorders other than atherosclerosis may cause attacks that are more or less indistinguishable from true TIAs as just defined. They are listed in Box 24.10.1.2. These rare but im- portant causes are reason enough to order a CT or MRI scan of the brain in patients with cerebral TIAs (not necessarily in those with transient monocular blindness). A  chronic subdural haematoma should always be suspected in older people, especially if they are on anticoagulants. Hypoglycaemia should come to mind in patients with diabetes. Focal weakness may follow an epileptic seizure (Todd’s paralysis) and may be misdiagnosed as a TIA if the initial jerking is missed or misinterpreted. Tumours may also cause temporary deficits without focal epilepsy. Transient global amnesia is a disorder of memory possibly caused by migrainous vasospasm or venous con- gestion; although technically ischaemic in nature, it is not associated with an increased risk of stroke or other vascular disease. Prognostic implications of TIAs Without treatment, the risk of stroke after a TIA can be estimated at up to 20% in the first year and 7% in subsequent years, and the average risk of death, stroke, or myocardial infarction in the first five years at 10% per annum. Heart disease and stroke each account for about one-third of all deaths. It is important to recognize that the risk of stroke is highest soon after the first episode if patients are not treated urgently: 8% in the first week, 12% at 1 month, and 17% at 3 months. Patients at particularly high risk can be identified by means of the ABCD2 score (see ‘Further reading’): A for age (>60 years), B for blood pressure (>140/90 mm Hg), C for clinical features (2 points for unilateral weakness, 1 point for speech disturbance without weak- ness), and D for duration (2 points for >60 min, 1 point for >10 min) and for diabetes (1 point). The risk of stroke within 2 days is approxi- mately 8% in patients with a score of 6 or 7, 4% in those with a score of 4 or 5, and much less in the others. These risks are reduced by urgent medical treatment, particularly by antiplatelet treatment. Investigations in patients with cerebral ischaemia There is no great difference between searching for the cause of

a TIA and searching for the cause of an ischaemic stroke. Very early Box 24.10.1.1 Attacks that should generally not be regarded as definite TIAs • Any attack with loss of consciousness • Any attack with involuntary jerking (with the rare exception of limb shaking TIA due to low blood flow distal to a carotid occlusion) • Any attack with positive visual phenomena (bright lights, and so on), particularly if the symptoms progressed over minutes • Any attack with only one of the following: • numbness • dizziness (with or without spinning sensations) • double vision • slurred speech • unsteady walking Box 24.10.1.2 Disorders that may mimic genuine TIAs • Chronic subdural haematoma • Intracranial tumour (glioma, metastasis, meningioma) • Hypoglycaemia • Focal deficits following a partial epileptic seizure • Transient global amnesia • Myasthenia gravis

24.10.1 Stroke: Cerebrovascular disease 6015 CT or MRI is mandatory, mainly to exclude intracerebral haemor- rhage and the occasional structural lesion mimicking stroke and to demonstrate infarcts. Box 24.10.1.3 lists the major and con- tributory causes of TIA and ischaemic stroke, with corresponding investigations. In general, first-line investigations are full blood count, erythrocyte sedimentation rate (ESR), plasma glucose, creatinine and electrolytes, plasma lipids, ECG, duplex ultrasound scanning of the arteries in the neck, and unenhanced CT or MRI of the brain. Ideally, CT or MR angiography of the intracranial arteries and the posterior circulation should also be performed, both in major stroke (to help determine the need for thrombolysis or thrombectomy) and in TIA and minor stroke (to understand aetiology and optimize secondary prevention). Prolonged ambu- latory cardiac rhythm monitoring (e.g. 7-day R-test) is indicated to identify patients with paroxysmal atrial fibrillation if no other clear cause of the TIA or stroke is found. Evidence on the usefulness of routine echocardiography is limited and conflicting. Diagnosis of cerebral infarction Distinction from other types of stroke From a practical point of view, the first step is to distinguish is- chaemic stroke from intracerebral haemorrhage. In the past, when a certain distinction could be made only at operation or postmortem examination, a decreased level of consciousness and headache were considered typical of intracerebral haemorrhage. After CT became available in the 1970s, it soon became clear that smaller haemorrhages are not associated with headache and drow- siness. Given that 4 out of 20 strokes are haemorrhagic, and on the assumption that half of all haemorrhages lack distinctive clin- ical features, a diagnosis of cerebral infarction based on clinical features alone will be wrong in approximately every tenth case. Even complex clinical scoring methods hardly improve on this error rate. On CT, acute parenchymal haemorrhage is of higher density than normal brain tissue (see Fig. 24.10.1.6). The hyperdensity occurs immediately—it is caused by the iron molecules in haemo- globin. In small haemorrhages, the hyperdensity can be lost within two to three days, such that the CT appearances are then easily confused with cerebral infarction. It is important therefore that brain imaging is performed quickly even in minor strokes. With the advent of very iron-sensitive MR imaging techniques, such as gradient-echo imaging, signs of previous haemorrhages are much easier to spot. These techniques often also identify multiple small areas of iron-deposition, which are thought to be ‘microbleeds’. These lesions are associated with hypertension and with cerebral amyloid angiopathy. Signs of infarction are more difficult to detect at an early stage. In the first decade of CT this was not possible until after three days, when frank tissue necrosis caused a hypodense lesion on the scan. With improved CT technology, subtle early signs of cerebral in- farction have been recognized, at least when the area of infarction is large. These features include loss of normal differentiation be- tween grey and white matter (such as the normal outline of the insular ribbon and the lentiform nucleus) (Fig. 24.10.1.3) and ef- facement of cortical sulci. With the advent of diffusion-weighted MR imaging, which is very sensitive to early changes in cerebral infarction, it is

much easier to identify acute ischaemia, but not all acute stroke patients will tolerate an MRI scan and MRI is contra- indicated in about 10% of older patients due to metallic implants of various kinds. Within the first few days, CT will show that the area of infarc- tion changes into a slightly hypodense, ill-defined, and somewhat swollen lesion; towards the end of the first week it becomes more Box 24.10.1.3 Major and contributory ‘causes’ of transient ischaemic attack (TIA) or ischaemic stroke, with corresponding investigations Investigations marked with an asterisk (*) have proven implications for management. Arterial atheroma • Internal carotid artery in the neck—duplex ultrasound study • Intracranial arteries—angiogram (with MR, CT, or catheter) Small vessel disease • Aorta—transoesophageal echocardiography • MRI brain imaging to identify asymptomatic lacunes and microbleeds Other arterial disease • Congenital arterial anomalies—angiogram (with MR, CT, or catheter) • Moya-moya syndrome—angiogram (with MR, CT, or catheter) • Arterial dissection—MRI; angiogram (with MR, CT, or catheter) • Giant cell arteritisa—ESR*, temporal artery biopsy* • Systemic vasculitis—antinuclear antibodies*, tissue biopsy* • Embolization from arterial aneurysms—MRI; angiogram (with MR, CT, or catheter) • Cholesterol embolization syndrome—biopsy of skin, muscle, or kidney • Meningitis, encephalitis—cerebrospinal fluid*, brain biopsy* • Drugs of abuse—toxicological screening of urine • Genetic conditions (mitochondrial encephalomyopathy, lactic acid- osis, and stroke-like episodes (MELAS), analysis of mitochondrial or nuclear DNA, cerebral autosomal dominant arteriopathy with sub- cortical infarcts and leukoencephalopathy (CADASIL), Fabry’s disease), α-galactosidase A* • Irradiation • Migraine Embolism from the heart • Atrial fibrillation—ECG*; long-term monitoring of heart rhythm* • Recent myocardial infarction—ECG* • Rheumatic valvular disease—echocardiogram* • Infective endocarditis—echocardiogram*, blood cultures* • Open foramen ovale—venography*, echocardiogram, bubble TCD • Atrial myxoma—echocardiogram* Haemostatic factors • Polycythaemia or iron deficiency anaemia —haematocrit* • Sickle cell disease—peripheral blood smear, sickling test • Thrombocytosis—platelet count* • Leukaemia—white cell count*, morphological analysis* • Disseminated intravascular coagulation—platelet count, prothrombin, and activated partial thromboplastin times, fibrinogen, fibrinogen degradation products, D-dimers Contributing risk factors • Hypertension—serial measurement of blood pressure* • Diabetes—fasting glucose*, HbA1c? • Hypercholesterolaemia—plasma cholesterol* • Hyperhomocysteinaemia—plasma homocysteine level ESR, erythrocyte sedimentation rate. a Only with involvement of optic nerve or occipital lobe.

 clearly demarcated and hypodense (Fig. 24.10.1.3). Occasionally there may be massive swelling with the potential for brain hernia- tion or haemorrhagic transformation. During the second week the infarct may again gradually increase in density, because the degrad- ation products of necrotic brain tissue more readily absorb X-rays; in the third and fourth weeks the infarcted area may even become isodense, being temporarily almost indistinguishable from normal brain, the so-called ‘fogging effect’. Eventually a sharply demarcated, atrophic, hypodense (similar to cerebrospinal fluid) defect remains. It is not always possible to determine how old an infarct is, or to dis- tinguish it from the scar of a haemorrhage that occurred weeks or years before. Intravenous injection of X-ray contrast may in the first weeks cause some enhancement of adjacent brain tissue. The proportion of patients in whom CT shows an appropriate in- farct depends not only on the time of scanning and the generation of the scanner, but also on the size of the infarct and its location; even- tually more than 90% of infarcts will show up. MRI is especially useful for demonstrating small infarcts and lesions in the posterior

fossa; diffusion-weighted imaging is also much more sensitive than CT in the early phases of brain is- chaemia. Signal changes on T2-weighted images occur after 6 to 8 h. Infarcts of any size are visible within minutes on diffusion-weighted imaging. The distinction from intracerebral haemorrhage is less ob- vious than on CT, but after a few hours the paramagnetic effects of deoxyhaemoglobin can be identified. Classification of cerebral infarction Time course has often been the guiding principle in the classification of stroke in the era before brain imaging. From the point of view of management and prognosis, however, the distinction between 'pro- gressive stroke' and 'completed stroke' is hardly useful, let alone that between 'permanent stroke' and 'reversible ischaemic neurological deficit' (a kind of 'extended TIA' with complete recovery within 3 or 6 weeks, depending on local convention). What counts is the even- tual severity of the functional deficit and, conversely, the remaining functions that are at risk. The anatomical classification distinguishes infarcts according to the territory of major cerebral arteries: in the cerebral hemi- spheres infarcts can be located in the supply areas of anterior cere- bral artery, middle cerebral artery, or posterior cerebral artery, or in the border zones between these three main branches; the cere- bellum and brainstem are supplied by branches of the vertebral arteries and the basilar artery. The problems are that there is little if any relationship with handicap, mostly no distinction is made between partial and complete infarcts in a given territory, and the boundaries between different territories vary substantially be- tween individuals. Classification according to the cause of ischaemic stroke is of interest for studies aiming to describe or influence the pathophysio- logical background of strokes. The so-called TOAST classification, for example, distinguishes five subtypes of ischaemic stroke: (1) large artery atherosclerosis, (2) cardioembolism, (3) small vessel oc- clusion, (4) stroke with other specific cause, and (5) stroke with un- determined cause. At present about 40% of patients would currently end up in the category 'undetermined', even in specialized stroke services. Also, the classification may change according to the extent of ancillary investigations. Finally, and most important, the system is not suited for assessing the severity of stroke. Rehabilitation specialists are more interested in the functional abilities of patients than in the niceties of neurological nosology. They mostly grade patients' disability on a scale for activities of daily life (such as the Barthel scale, which ranks 10 in-house activ- ities in hierarchical order, from bowel continence to taking a bath), or on a scale that includes some elements of social role fulfilment ('handicap'), such as the Rankin scale (Table 24.10.1.1). A system that strikes a useful compromise between the restric- tions of lifestyle and the anatomical point of view is the classification of the Oxfordshire Community Stroke Project. Four categories are distinguished: (a) (b) Fig. 24.10.1.3 Acute cerebral infarction in a 78-year-old man. (a) CT scan about 6 h after symptom onset. In the left brain hemisphere (on the reader's right) there are subtle changes in the region of the basal ganglia: other than on the normal side, it is difficult to distinguish the different brain nuclei and their separation by white matter. (b) CT scan 4 days after symptom onset shows marked hypodensity in the entire territory of the left middle cerebral artery.

 1 Total anterior circulation infarcts (TACIs), with both cortical and subcortical involvement, representing about one-sixth of all ischaemic strokes in the community 2 Partial anterior circulation infarcts (PACIs), with more restricted and predominantly cortical infarcts (one-third of all infarcts) 3 Posterior circulation infarcts (POCIs), clearly associated with the vertebrobasilar arterial territory (one-quarter) 4 Lacunar circulation infarcts (LACIs), confined to the territory of the deep perforating arteries (one-quarter) Although the classes are anatomically defined, they contain im- portant prognostic information: case fatality is highest by far in the TACI group and lowest by far in the LACI group. Syndromes of cerebral infarction

Occlusion of the internal carotid artery may cause no symptoms at all or infarction, at its worst in the entire territory of the ipsi- lateral anterior and middle cerebral artery (and sometimes of the posterior cerebral artery or contralateral anterior cerebral artery as well), depending on the presence of a complete circle of Willis and other collaterals. If arterial dissection is the cause of carotid occlusion, subadventitial bulging of the artery may cause Horner's syndrome and lower cranial nerve palsies, with or without infarc- tion. Occlusion of the anterior, middle, and posterior cerebral ar- teries may lead to complete or partial infarction in their respective territories, depending on collaterals at the surface of the brain. Obviously, branch occlusions cause smaller infarcts. What follows is a description of syndromes associated with complete infarction in the average territory of the main cerebral arteries, although there is much individual variation in practice. Middle cerebral artery infarcts, if complete, typically present with contralateral hemiplegia (most marked in the arm), sensory deficit, hemianopia, and cognitive defects such as aphasia (dominant hemisphere) or contralateral neglect (nondominant hemisphere). Massive infarction of the entire territory of the middle cerebral ar- tery may lead to massive brain swelling followed by herniation, es- pecially in young patients without cerebral atrophy. Occlusion of a vertebral artery involving the origin of the posteroinferior cerebellar artery causes Wallenberg's syndrome, with ipsilateral cerebellar ataxia through infarction of the inferior part of the cerebellum, and a—for students, slightly bewildering— combination of deficits from infarction of the dorsolateral me- dulla: decreased skin sensation in the ipsilateral half of the face and the contralateral half of the body; ipsilateral Horner's syndrome; ipsilateral weakness of the soft palate, larynx, and pharynx; and ro- tatory vertigo. The full basilar artery syndrome, with infarction of most of the pons and midbrain, consists of coma, tetraparesis including facial movements, and loss of all eye movements and of pupillary and cor- neal reflexes. There are two characteristic partial syndromes of the basilar artery. One is the locked-in syndrome (infarction of the base of the pons), with tetraparesis, including facial movements and loss of horizontal eye movements. Consciousness is preserved through sparing of the reticular formation, but patients can communicate only through vertical eye movements; these may not always be cor- rectly interpreted or even noticed. The other is the top-of-the-basilar syndrome, with variable combinations of hemianopia or complete cortical blindness (occipital lobes), amnesia (inferior temporal lobes) and vertical gaze palsies, pupillary disturbances, and hallu- cinations (perforating branches to the midbrain). The posterior cerebral artery syndrome may include hemianopia (occipital lobe), amnesia (lower temporal lobe), and oculomotor disorders or disturbances of language or visuospatial function, by involvement of perforating branches to the thalamus. Occlusion of a single perforating artery, one of the many that originate at right angles from a large parent artery to supply a small area in the deep regions of the brain or brainstem (Fig. 24.10.1.4), may be clinically silent, or cause a so-called 'lacunar syndrome'. A necessary condition for the clinical diagnosis of a lacunar syn- drome is the absence of 'cortical' deficits such as aphasia, neglect, Table 24.10.1.1 Modified Rankin scale (or Oxford Handicap Scale) for measuring outcome after stroke (but suitable for other purposes as well) Grade Description 0 No symptoms 1 Minor symptoms that do not interfere with lifestyle 2 Symptoms that lead to some restriction of lifestyle but do not interfere with the patient's capacity to look after himself 3 Symptoms that restrict lifestyle and prevent a completely independent existence 4 Symptoms that clearly prevent independent existence though no constant attention is required (patients are usually wheelchair-bound) 5 Totally dependent patient requiring constant attention, night and day (patients are often bed-bound) Infarcts in the area of the anterior cerebral artery cause contralateral hemiparesis, more marked in the leg than in the arm, with no or only mild sensory deficit. Other frontal lobe features include mutism, incontinence, and apathy or, conversely, disinhibition. Fig. 24.10.1.4

Small, deep infarct (‘lacune’) in a 63-year-old woman. CT scanning shows a small area of hypodensity (distinct from sulci) in the left brain hemisphere (on the reader’s right), just lateral to the internal capsule.

section 24 Neurological disorders 6018 hemianopia, or conjugate deviation of the eyes. The most common and archetypal form is pure motor stroke. In those cases, the small deep infarct strategically involves corticospinal fibres (pyramidal tract) to the motor neurons of the limbs, anywhere in its course. Analogous fibres to the facial nucleus in the pons may be affected as well. The infarct can be located in the corona radiata, adjoining the wall of the body of the lateral ventricle, or slightly more caud- ally, in the posterior limb of the internal capsule, or, less com- monly, in the pons or the medulla. Other ‘lacunar syndromes’ are sensorimotor stroke (corona radiata or internal capsule), pure sensory stroke (thalamus), and ataxic hemiparesis (usually the base of the pons). Lacunar infarcts in the brainstem may lead to an almost infinite range of syndromes, often with the name of a French 19th-century neurologist attached to it. Often such syn- dromes consist of an ipsilateral cranial nerve deficit and a contra- lateral hemiparesis.
Treatment of acute cerebral infarction Several interventions aim at removing (thrombectomy) or dissolving (thrombolysis) the occluding clot, or at least preventing it from growing (antiplatelet agents and anticoagulants). A different strategy, not yet proven in clinical trials, is to protect ischaemic brain tissue (neuroprotection by drugs or manipulation of physiological param- eters such as fever or hyperglycaemia). In addition, some underlying causes of stroke need urgent treatment, such as endocarditis. Before considering these specific measures, it is appropriate to consider the appropriate hospital setting in which stroke patients should be cared for. Stroke units compared with treatment
on general hospital wards A specially organized stroke unit can be a ward or team that exclu- sively manages stroke patients (a dedicated stroke unit) or a ward or team that provides a generic disability service (a mixed assess- ment or rehabilitation unit). According to a meta-analysis of 23 randomized trials, stroke unit care reduces the risk of death or in- stitutionalized care by 14%. The observed benefits are independent of patient age, sex, or stroke severity, and appeared to be better in stroke units based in a separate ward. No single element responsible for the benefits of organized stroke care has so far been identified, and probably there is none. The strength of stroke units lies in good clinical leadership and in the integration of multidisciplinary ef- forts: stroke physician, nursing staff, physiotherapists, occupational therapists, speech and language therapists, rehabilitation phys- icians, and social workers. With the evidence that thrombolysis and thrombectomy improve stroke outcome in a significant pro- portion of patients, there has been a move to develop hyperacute stroke units. Thrombolysis Restoration of blood flow, to reperfuse the ischaemic brain as soon as possible after the cerebral artery has been occluded, irrespective of its cause, should theoretically lead to reduction in the volume of brain damaged by ischaemia and to improvement in clinical out- come, analogous to myocardial infarction. The main agents tested so far in stroke are intravenous recom- binant tissue plasminogen activator (rt-PA) and intravenous streptokinase. Almost all patients in the trials were treated within 6 h of stroke onset. The evidence for efficacy is statistically signifi- cant for rt-PA, if administered within 4.5 h and after exclusion of intracerebral haemorrhage by CT. Even within this period, the adage is ‘the sooner, the better’. For patients treated within 90 min, the point estimates for survival with at most moderate disability im- proved from 54% in the placebo groups to 63% for patients in the rt-PA groups (absolute gain 9%), whereas for patients treated be- tween 91 and 180 min after stroke onset the gain was 7% (from 57% to 64%). Taken together, a benefit of 8% means that some 12 patients must be treated to

save a single patient from death or the nursing home. These calculations have already taken into account the fact that there is a risk of secondary haemorrhage after treatment with rt-PA. More convenient single injection thrombolysis drugs, such as tenectoplase, are currently in large-scale clinical trials. There are, however, many contraindications to thrombolysis in view of the risk of cerebral haemorrhage, and only a minority of patients admitted with cerebral infarction can be treated with thrombolysis. Thrombectomy Thrombectomy is the retrieval of clot from an occluded artery by one of several intra-arterial devices. In 2015, several randomized trials reported highly consistent results showing that thrombectomy resulted in better outcomes than control in patients who had acute stroke and an appropriate arterial occlusion on vascular imaging. Thrombectomy was beneficial as a primary treatment and also in patients who had a persisting vessel occlusion after thrombolysis. However, the logistics of providing a 24/7 thrombectomy service are substantial and may be beyond the reach of many healthcare systems. Antiplatelet agents More than 99% of the evidence from randomized trials in treat- ment of acute stroke relates to aspirin. The pooled results of two very large trials with aspirin (160–300 mg), started within 48 h of onset, concluded that 13 fewer patients are dead or dependent for every 1000 patients treated. In some 800 patients who had been inadvertently randomized after a haemorrhagic stroke there was no evidence of net hazard. Much of the benefit of aspirin is in preven- tion of early recurrent stroke rather than in reducing the severity of the existing stroke. Anticoagulants Anticoagulants tested in clinical trials are standard unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anti- coagulants, and thrombin inhibitors. There is no evidence that anti- coagulant therapy reduces the odds of being dead or dependent at the end of follow-up. Neuroprotective agents There are many steps in the destructive cascade between vessel occlusion and irreversible cell death where pharmacological intervention might be beneficial, at least theoretically. The pharma- ceutical industry has developed several compounds for clinical

 development and testing. There is no doubt that in animal models many neuroprotective agents, given either before or after the onset of ischaemia, reduce the area of cerebral infarction. So far, none of these agents has been proven to reduce disability in patients, despite dozens of clinical trials. Surgical decompression of space-occupying infarcts To prevent brain herniation and death from supratentorial infarction, a large part of the skull vault can be removed by hemicraniectomy. A pooled analysis (three trials) of 93 patients randomized within 48 h of stroke onset showed not only that the case fatality rate was much lower in operated patients (22%) than in patients who were treated conservatively (71%), but also that operated patients sur- vived significantly more often (43%) with mild or moderate dis- ability (modified Rankin grade 3 or less, see Table 24.10.1.1), against 21% in the conservative group. This has to be weighed against an increased proportion of survivors with severe disability (modified Rankin grade 4 or 5): 35% against 7%. With operations for space- occupying infarcts of the cerebellum there is no controlled evidence, but less uncertainty. Without surgery swelling of a cerebellar infarct can be fatal, whereas the deficits after surgical evacuation are sur- prisingly mild. In some patients it is sufficient to relieve obstructive hydrocephalus by external ventricular drainage. Secondary prevention of ischaemic stroke In the long-term management of patients with TIAs or moderately disabling ischaemic strokes, control of lifestyle factors is a primary concern: cessation of smoking, reducing weight if overweight, and daily exercise. Specific measures to reduce the risk of threatened stroke are mostly pharmacological. Carotid endarterectomy or stenting is the only local treatment that is of proven value. Carotid endarterectomy and stenting This operation was increasingly performed from the 1960s onwards,

but not until the 1980s were two randomized trials performed, one in Europe, and one in North America. In patients with severe, symp- tomatic carotid stenosis (70–99% lumen diameter reduction) the risk of disabling or fatal stroke substantially decreases after end- arterectomy. On average, about six patients need to undergo sur- gery to prevent one ipsilateral ischaemic stroke within 5 years. This basic risk difference varies with age and sex, and it levels off after 3 or more years from randomization (i.e. 3.5 years after the qualifying event). It should be kept in mind that carotid endarterectomy is in- dicated in only a minority (<10%) of patients with TIAs or moder- ately disabling ischaemic strokes: the attacks have to be in the carotid territory, the patients should be fit and willing to undergo the oper- ation, and the angiogram should show an accessible stenosis of over 70% at the carotid bifurcation. A possible alternative for endarterectomy is carotid stenting, with or without devices to prevent emboli being carried downstream during the procedure. Despite the less invasive nature of this pro- cedure, the perioperative risk of stroke is higher than or endarterec- tomy, although stenting appears to be as durable as endarterectomy in reducing the subsequent long-term risk of stroke. For the demonstration of severe carotid stenosis, it is no longer necessary to perform catheter angiography, at least if the results of duplex ultrasound agree with those of CT angiography or MR angiography. Antiplatelet drugs The preventive effect of aspirin, in different doses, has been studied in placebo-controlled randomized trials in over 8000 patients after a TIA or moderately disabling stroke. There is virtually no differ- ence between the risk reduction for daily doses between 30 mg and 1300 mg. The overall relative reduction in long-term risk of stroke is about 13% (95% confidence interval 6–19%), but most of that benefit accrues in the first 12 weeks and the risks and benefits of longer-term treatment versus gradual withdrawal ae uncertain. Side effects of aspirin, mainly indigestion, nausea, heartburn, and gastrointestinal bleeding, are more common as the dose is higher. Addition of dipyridamole 200 mg twice daily to aspirin provides a further risk reduction of approximately 18%, compared with aspirin alone. Headache is a common side effect of dipyridamole; it can be avoided by starting with smaller doses. Clopidogrel, a thienopyridine derivative, is marginally more ef- fective than aspirin, with a relative risk reduction of 8.7% (95% con- fidence interval 0.3–16.5), whereas the combination of clopidogrel and aspirin has no advantage over aspirin alone; clopidogrel should be prescribed only in patients who are intolerant to aspirin. A large trial comparing clopidogrel with aspirin plus dipyridamole in long-term secondary prevention of stroke showed no difference in effectiveness. Anticoagulants With sources in the heart, mostly from atrial fibrillation, coumadin anticoagulants (INR 2.5–4) are the first choice in the absence of contraindications; no evidence exists for a fixed age limit. In pa- tients with a presumed arterial cause of cerebral ischaemia, anti- coagulants may prevent some ischaemic events, but this benefit is offset or even outweighed by the risk of haemorrhages, especially in the brain, depending on the intensity of anticoagulation. In recent years, several new oral anticoagulants have been developed and have been shown to be at least as effective as coumadin anticoagulants in preventing ischaemic stroke and systemic embolism and to have a lower risk of intracranial bleeding. Statins The protective effect on major cardiovascular events of statins, or, with the full name of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, has been proved in clin- ical trials involving more than 100, 000 patients with cardio- vascular disease or risk factors, including cerebral ischaemia. The reduction in the 5-year incidence of major coronary events, coronary revascularization, and stroke is about 20% per mmol/ litre reduction in low-density lipoprotein (LDL)-cholesterol, largely irrespective of the initial lipid profile or other presenting characteristics. Antihypertensive drugs Observational studies provide overwhelming evidence that the level of blood pressure is by far the most powerful risk factor for

section 24 Neurological disorders 6020 stroke. That lowering the blood pressure prevents stroke has also been confirmed by several controlled clinical trials in primary pre- vention as well as in patients with previous TIA or stroke. In indi- viduals with a history of stroke or TIA, a blood pressure-lowering regimen reduces the risk of stroke, regardless of whether or not the blood pressure at baseline was considered too high. The reduction of the stroke risk ranges from one-quarter to one-half, depending on the degree of blood pressure lowering. In terms of the choice of antihypertensive drug-class, there is some evidence that calcium channel blockers and diuretics are most effective in prevention of stroke, with ACE-inhibitors being less effective and β-blockers least effective. In conclusion, the optimal strategy for secondary prevention of stroke depends on the probable source of embolism. In patients with atrial fibrillation oral anticoagulants are the preferred treat- ment. Patients in sinus rhythm should be treated with a trio of drugs: an antiplatelet agent, a statin, and sufficient antihypertensive treatment to control any hypertension. In most cases, baseline values for cholesterol or blood pressure should not influence the decision to administer statins and antihypertensive drugs, only the choice of the dose and subsequent increases in intensity of treat- ment. In addition, patients with ischaemic events in the carotid territory should be investigated noninvasively for the presence of severe stenosis in the ipsilateral internal carotid artery, with a view to carotid endarterectomy, or stenting if there are reasons to avoid endarterectomy. Venous occlusive disease The advent of noninvasive brain imaging methods in the last few decades has resulted in increased recognition of cerebral venous thrombosis. Before that time, physicians only rarely considered the diagnosis in patients with otherwise unexplained headache, focal deficits, seizures, impaired consciousness, or combinations of these features. Causal factors Unlike arterial occlusion, cerebral venous thrombosis is only rarely (in c.10%) associated with damage to the vessel wall—by infection, tumour growth, or trauma. Much more frequent causes are inherited disorders of coagulation. The most common form is factor V Leiden mutation, found in some 20% of patients without other causes. In 20% of patients no causal factors can be identified. Often there is not a single cause but a combination of contrib- uting factors (e.g. the post-partum period and protein S deficiency; pregnancy and Behçet’s disease; or oral contraceptive drugs and the factor V Leiden mutation). The risk of cerebral venous thrombosis in the post-partum period increases with maternal age and with the performance of caesarean section. In neonates, cerebral venous thrombosis is usually associated with acute systemic illness, such as shock or dehydration; in older chil- dren the most frequent underlying conditions are local infection (the leading cause before the antibiotic era), coagulopathy, and in Mediterranean countries Behçet’s disease. Diagnosis of cerebral venous thrombosis The clinical features of cerebral venous thrombosis consist essen- tially of headache, focal deficits, seizures, and impairment of con- sciousness, in various combinations and degrees of severity. The symptoms and signs depend on which sinus is affected, and for a large part on whether the thrombotic process is limited to the dural sinus or extends to the cortical veins. In the case of the superior sagittal sinus, which is affected in 70 to 80% of all cases, cerebral venous thrombosis alone will lead to the syndrome of intracranial hypertension (i.e. headache and papilloedema). Up to 30% of patients with so-called ‘ideopathic intracranial hypertension’ may in fact have sinus thrombosis—most commonly men and nonobese women. Papilloedema can cause transient visual obscurations and sometimes irreversible constric- tion of visual fields, beginning in the inferonasal quadrants. The increased pressure of the cerebrospinal fluid may also give rise to cranial nerve VI palsies, and sometimes to other cranial nerve deficits. The onset of the headache is usually gradual, but in up to 15% of patients it is sudden and may initially suggest the diagnosis of a ruptured aneurysm. Involvement of cortical veins causes one or more areas of venous infarction,

with or without haemorrhagic transformation. If the affected veins drain into the superior sagittal sinus the venous in- farcts are typically located near the midline in the rolandic and parieto-occipital regions, often on both sides. In the case of the lateral sinus the venous infarct is usually located in the posterior temporal area. Clinically the infarcts manifest themselves through epileptic seiz- ures or focal deficits such as hemiparesis or dysphasia. If unilateral weakness develops (with thrombosis originating in the superior sa- gittal sinus), it tends to predominate in the leg, in keeping with the parasagittal location of most venous infarcts. Obstruction of cortical veins draining into the posterior part of the superior sagittal sinus or into the lateral sinus will commonly lead to hemianopia, dysphasia, or a confusional state. Impairment of consciousness may result from multiple lesions in the cerebral hemispheres, or from transtentorial herniation and compression of the brainstem. Either epilepsy or a focal deficit is a presenting feature in 10–15% of patients; in the course of the illness seizures occur in 10–60% of reported series, and focal deficits in 30–80%. Involvement of the cortical veins alone, without sinus thrombosis and its associated signs of increased cerebrospinal fluid pressure, is an extremely rare occurrence. Thrombosis of the deep venous system, including the great vein of Galen (great cerebral vein), may lead to bilateral haemorrhagic infarction of the corpus striatum, thalamus, hypothalamus, ventral corpus callosum, medial occipital lobe, and upper part of the cerebellum. In those cases, the clinical picture is often dominated by deep coma and disturbance of eye movements and pupillary reflexes. Investigations CT will readily show ‘venous’ infarcts. These do not correspond to a known arterial territory, and often show haemorrhagic trans- formation (Fig. 24.10.1.5); they are sometimes bilateral, in the parasagittal area, supra- as well as infratentorial, or in the deep

 regions of the brain. In addition, CT will often provide evidence of the underlying sinus thrombosis: the hyperdense sinus sign or, less reliable, the so-called empty δ-sign after injection of intravenous contrast material. MRI has made catheter angiography redundant in the diagnosis of cerebral venous thrombosis. It is not sufficient to rely on non- visualization of a cerebral sinus on MR venography, because this may represent hypoplasia. Demonstration of the thrombus itself is essential, but this depends very much on the interval from disease onset. Three stages can be distinguished. In the acute stage (days 1–5) the thrombus appears strongly hypointense in T2-weighted im- ages and isointense in T1-weighted images. In the subacute stage (up to day 15) the thrombus signal is strongly hyperintense, initially on T1-weighted images and subsequently also on T2-weighted images (Fig. 24.10.1.5). The third stage begins 3 or 4 weeks after symptom onset: the thrombus signal becomes isointense on T1-weighted im- ages but on T2-weighted images it remains hyperintense, although often inhomogeneous. Recanalization may occur over months in up to one-third of patients, but persistent abnormalities are common and do not signify recurrent thrombosis. Treatment and prognosis Anticoagulant treatment is plausible, but the evidence from con- trolled clinical trials is sparse. In the acute phase heparin (either by intravenous route or, subcutaneously, as low-molecular-weight hep- arin) seems preferable to oral anticoagulants, because its intensity can be closely monitored. The evidence for heparin treatment rests on no more than 80 randomized patients; there is a nonsignificant trend towards better outcome in treated patients. At least heparin treatment seems safe, even in patients with haemorrhagic infarcts. Local thrombolysis via endovascular catheters has been performed only in uncontrolled studies. Death rates in different series range between 5% and 30%, and probably depend more on case mix than on treatment. Residual deficits consist mostly of hemispherical deficits or visual impair- ment from optic atrophy. The risk of recurrence has seldom been systematically addressed; it is probably of the order of 10%. It seems wise to advise other

means of contraception than the combined oral contraceptive pill (see Chapter 9.9). In women with a peripartum episode of cerebral venous thrombosis, the available evidence does not warrant the advice to avoid a further pregnancy, although in patients with the factor V Leiden mutation the risk of a recurrent episode is probably higher than average. Long-term anticoagulation is usually recom- mended in patients with a definite thrombophilia or in those with previous venous thrombosis in other territories. Primary intracerebral haemorrhage Causes of primary intracerebral haemorrhage In most cases there is no single cause for primary intracerebral haemorrhage. Even in the classic example of a so-called hypertensive haemorrhage in the region of the basal ganglia, the question remains about which anatomical or other factors distinguished this patient from others, with similar degrees and duration of hypertension but without brain haemorrhage. Even a combination of recognized ‘causes’, such as that of hypertension and anticoagulants, does not invariably lead to intracerebral haemorrhage. In general, therefore, it is likely that several causal factors combine. These can be broadly distinguished into three categories (Box 24.10.1.4): anatomical fac- tors (lesions or malformations of brain vasculature), haemodynamic factors (blood pressure), and haemostatic factors (to do with platelet function or the coagulation system). Abnormalities of the vascular (b) (a) Fig. 24.10.1.5 Cerebral venous thrombosis in a 27-year-old woman. (a) This CT scan shows a small infarct with haemorrhagic transformation in the right brain hemisphere, adjacent to the top of the lateral ventricle. (b) Magnetic resonance imaging, focused on venous structures, shows nonfilling of the frontal part (on the reader’s left) of the superior sagittal sinus.

section 24 Neurological disorders 6022 system account for most haemorrhages. The type of underlying ab- normality varies with age: below the age of 40 arteriovenous or cav- ernous malformations are the most common single causes, whereas between 40 and 70 the most frequent sources are ruptured perfor- ating arteries (deep haemorrhages); in older people one also finds haemorrhages in the white matter (‘lobar’ haemorrhages), com- monly attributed to amyloid angiopathy. ‘Hypertensive’ intracerebral haemorrhage ‘Hypertensive’ intracerebral haemorrhage results from degenerative changes in small perforating vessels, in the deep regions of the brain (basal ganglia and thalamus—Fig. 24.10.1.6), or in the cerebellum or brainstem. Risk factors other than hypertension are age, male sex, and high alcohol intake. Microaneurysms occur on these vessels but are not necessarily the only site of rupture. There is a high risk of early, rapid expansion of intracerebral haematomas, sometimes seen during a single scanning procedure or on serial scanning. A stable phase is usually reached in a matter of hours. Deep brain haemorrhages are not always a one-off event. The recur- rence rate in the first year is 7%, against 2% per year over the subse- quent 6 years, but is reduced by intensive control of any hypertension. Amyloid angiopathy This condition accounts overtly for about 10% of intracerebral haem- orrhages, but its significance has probably been underestimated in the pre-MRI era. Its frequency rises with age, but so does that of ‘hypertensive’ haemorrhage. The underlying abnormality consists of patchy deposits of amyloid in the muscle layer of small and medium- sized cortical arteries of the occipital, parietal, and frontal lobes. Amyloid can also be found in asymptomatic individuals, the propor- tion increasing with age. It is not found outside the brain and does not represent generalized amyloidosis. Haemorrhages associated with amyloid angiopathy typically occur at the border of the grey and white matter of the cerebral hemispheres. Recurrent haemorrhage associated with amyloid angiopathy is much more common than with ‘hypertensive’ small vessel disease. Hereditary forms of amyloid angiopathy account for only a small minority of all cases. Possible manifestations of amyloid angiopathy other than haem- orrhage are transient episodes of focal

neurological deficits (amyloid spells), and also intellectual deterioration, associated with diffuse demyelination of the subcortical white matter (leucoaraiosis). Cerebral arteriovenous malformations Arteriovenous malformations (AVMs) are tangles of dilated ar- teries and veins, without a capillary network between them. On angiography, they are recognizable by large feeding arteries and rapid shunting of blood to enlarged and tortuous veins, via a cen- tral nidus of dilated vessels. Haemorrhage is the initial clinical manifestation in 50–60% of symptomatic AVMs. Other clinical features include epileptic seizures, headaches, and progressive neurological deficits. Demonstrable AVMs are the most common single cause of intracerebral haemorrhage in patients under 45 years (c. 30%). In 10–20% AVMs are associated with thin-walled saccular an- eurysms. These occur on peripheral feeding arteries, not at the classic sites at the circle of Willis, and are likely sources of bleeding. In AVMs in which one or more aneurysms have formed, the an- nual risk of rebleeding is as high as 7%, against 2–3% per annum for other AVMs. If there is no associated aneurysm, the site of rupture is mostly on the venous side of the malformation. Box 24.10.1.4 Causes of primary intracerebral haemorrhage Anatomical factors • Lipohyalinosis (complex small vessel disease) and microaneurysms • Cerebral amyloid angiopathy • Saccular aneurysms • Cerebral arteriovenous malformations • Cavernous angiomas • Venous angiomas • Telangiectasias • Dural arteriovenous fistulae • Haemorrhagic transformation of an arterial infarct • Intracranial venous thrombosis • Septic arteritis and mycotic aneurysms • Moya-moya syndrome • Arterial dissection • Caroticocavernous fistula Other factors • Arterial hypertension • Migraine • Haemostatic factors • Anticoagulants • Antiplatelet drugs • Thrombolytic treatment (for nonneurological indications) • Clotting factor deficiency • Leukaemia and thrombocytopenia • Intracerebral tumours • Alcohol • Amphetamines • Cocaine and other drugs • Vasculitis • Trauma (‘Spät-Apoplexie’) Fig. 24.10.1.6 Primary intracerebral haemorrhage in a 52-year-old man. This CT scan shows a hyperdense lesion in the right thalamus; the haemorrhage has ruptured into the ventricular system.

 Cavernous malformations Cavernous malformations consist of sharply demarcated areas with widely dilated and thin-walled vascular channels, without intervening brain tissue. They are often asymptomatic and are en- countered in 0.5% of routine post-mortem examinations, in the white matter or cortex of a cerebral hemisphere in about one-half of all cases, in the posterior fossa in one-third, and in the basal ganglia or thalamus in one-sixth. If a cavernous malformation is at all symp- tomatic, seizures are at least as common a manifestation as haem- orrhage. The annual risk of haemorrhage in patients in whom the lesion presents with seizures or focal deficits is rather low, between 0.25% and 0.6%. After a first rupture, rebleeding is more frequent, around 4.5% per annum. Haemorrhages from a cavernous malfor- mation are rarely fatal. Familial forms of the disorder occur in several countries around the world, and should be suspected if multiple lesions are found. Several specific genetic defects have now been identified and should be tested for in patients with a strong family history or multiple malformations. Diagnosis of primary intracerebral haemorrhage The history sometimes suggests the cause of the haemorrhage. Previous seizures should raise suspicions about the presence of an AVM, cavernous malformation, or tumour. Amyloid angiopathy should come to mind in patients over 65 years of age with a history of TIAs, intellectual deterioration, or both. A record of long-standing hypertension indicates small vessel diseases as the most probable underlying condition in a patient with a haematoma in the basal ganglia or in the posterior fossa; on the other hand, hypertension is so common that it may coexist with other conditions. If the pa- tient is known to have had cancer, haemorrhage into a brain me- tastasis is a possibility. The use of oral

anticoagulants is a vital piece of information in patients with intracerebral haemorrhage, because their action should be neutralized as soon as possible. It is equally important to know about the use of recreational drugs, particularly cocaine and amphetamines. Finally, the circumstances preceding intracerebral haemorrhage may help to identify its cause, such as puerperium (intracranial venous thrombosis, choriocarcinoma) or neck trauma (dissection of the vertebral or carotid artery). The physical examination will provide rather few clues to the cause of an intracerebral haemorrhage, except petechiae or bruising, which indicate a generalized haemostatic disorder, signs of malig- nant disease such as cutaneous melanoma, a collapsed lung or en- largement of the liver or spleen, or telangiectasias in the skin and mucous membranes. Finding a high blood pressure on admission is the rule, but only in about 50% is there evidence of long-standing hypertension. Retinal haemorrhages indicate intracranial bleeding in general, most often subarachnoid haemorrhage. Heart mur- murs may be coincidental but should at least raise the possibility of infective endocarditis, as should the finding of needle marks in possible drug addicts. The neurological examination will show focal deficits corresponding to the site of the lesion, with or without a de- creased level of consciousness. Investigations should start with the usual tests of blood and serum. These will sometimes uncover a cause of intracerebral haem- orrhage, such as a low platelet count or massive liver damage. Brain imaging (CT or MRI) is the single most important investigation in patients with suspected intracerebral haematomas. The location of the haematoma may to some extent indicate the underlying cause. Intraventricular extension of the haemorrhage occurs relatively often with deep, ‘hypertensive’ haemorrhages. A grossly irregular margin of a lobar haematoma in older patients suggests amyloid angiopathy, as do multiple or recurrent haemorrhages in the white matter. Intracranial venous thrombosis should be suspected with irregularly shaped haemorrhages in the parasagittal region. Repeat brain CT after injection of contrast may pick up underlying lesions. Sometimes these can be identified only weeks later, when the lesion is no longer obscured by mass effects. Treatment of primary intracerebral haemorrhage Factors predicting the chances of survival of patients with primary intracerebral haemorrhage are: level of consciousness (Glasgow Coma Scale); age; volume of haematoma (poor prognosis if supratentorial haematoma more than 50 ml), subsequent expansion of the haematoma, and intraventricular extension of haemorrhage (poor prognosis if volume >20 ml). The possible interventions out- lined next, of course, apply only to patients who have a chance of survival. In patients on oral coumadin anticoagulants the first step is intra- venous injection of 10–20 mg of vitamin K, at not more than 5 mg/ min, followed by infusion of a concentrate of the coagulation factors II, VII, IX, and X, or of fresh frozen plasma. Specific agents for re- versal of the newer oral anticoagulants are also in development. Intracranial pressure is often raised. Factors other than the local effects of the haematoma may contribute, such as fever, hypoxia, hypertension, seizures, and elevations of intrathoracic pressure. An unsolved question is the use, in comatose patients, of monitoring and, if judged appropriate, lowering intracranial pressure. There are many believers in this area but few controlled studies. Insertion of a ventricular catheter may be a definitive measure in patients with cerebellar haemorrhage and no signs of direct compression of the brainstem. For surgical treatment of supratentorial haematoma, randomized trials have failed to show benefit, including those employing endo- scopic evacuation. In patients with cerebellar haematomas there is no doubt that surgical evacuation can be life-saving, often with sur- prisingly few neurological sequelae. Sound indications for evacu- ation of a cerebellar haematoma are the combination of a depressed level of consciousness with signs of progressive brainstem compres- sion (unless all brainstem reflexes have been lost for more than a few hours, in which case a fatal outcome is unavoidable), or haematoma greater than 3–4 cm. If the patient has a depressed level of

conscious- ness and hydrocephalus, without signs of brainstem compression and with a haematoma less than 3 cm, ventriculostomy can be car- ried out as an initial (and sometimes only) procedure. Subarachnoid haemorrhage Causes of subarachnoid haemorrhage Ruptured aneurysms are by far the most common source of nontraumatic subarachnoid haemorrhage, in about 85%. Around

section 24 Neurological disorders 6024 10% are nonaneurysmal peri-mesencephalic haemorrhages, the re- maining 5% is made up by rarities (Box 24.10.1.5). Cerebral aneurysms are not congenital; they develop during the course of life. Therefore, aneurysmal haemorrhage in a child is extremely rare. The aneurysms are saccular in shape and mostly arise at sites of arterial branching at the base of the brain, at or near the circle of Willis (Fig. 24.10.1.7). It is largely unknown why some adults develop aneurysms. There are families with two or more affected first-degree relatives, but these account for less than 5% of all subarachnoid haemorrhages. Many classic risk factors for stroke in general also apply to subarachnoid haemor- rhage: smoking, hypertension, heavy drinking, and oral contra- ceptives. Not all aneurysms rupture. Their prevalence can be estimated, from angiographic studies (for other purposes) and post-mortem studies at approximately 2–3% in middle age, up to 5% at the end of life. On the assumption that this proportion is 1% for a standardized population across all age groups, and given that the incidence of subarachnoid haemorrhage is approximately 6 per 100 000 (of the entire population), the annual risk of rupture of an aneurysm is about 0.6%. Nonaneurysmal perimesencephalic haemorrhage is a distinct and benign variety of subarachnoid haemorrhage, in which the distribution of extravasated blood on the brain CT scan is different from that with aneurysms, in the cisterns around the midbrain or ventral to the pons. The angiogram is completely normal, and the long-term outcome is invariably excellent. This subtype con- stitutes 10% of all subarachnoid haemorrhages and two-thirds of subarachnoid haemorrhages with a normal angiogram. Diagnosis of subarachnoid haemorrhage The key feature in the history is that of a sudden, severe, and un-usual headache. In 50% there is loss of consciousness at onset; the headache may emerge only later in these patients. The diagnosis is most difficult in patients with headache as the only feature. In general practice, sudden-onset forms of common headaches (‘thunder-clap’ headache) outnumber ruptured aneurysms. The incidence of aneurysmal haemorrhage being about 6 per 100 000 population per year, the average general practitioner will, on average, see one such patient every 8 years. There are no single or combined features of the headache that distinguish reliably and at an early stage between subarachnoid haemorrhage and innocuous types of sudden headache. The physical examination is unhelpful in patients with headache alone, without loss of consciousness or focal deficits. Neck stiffness takes about 6 h to develop, so its absence soon after the onset does not exclude the diagnosis of subarachnoid haemorrhage at all. CT brain imaging is the most important investigation in sus- pected subarachnoid haemorrhage. This will show extravasation of blood in the basal cisterns of the brain in at least 95% of patients with a ruptured aneurysm, if the scan is performed within 3 days (see Fig. 24.10.1.7). After that interval the sensitivity of CT quickly decreases. In patients with a negative CT scan but a convincing history, lumbar puncture is indicated. If the cerebrospinal fluid is blood stained, it is essential to distinguish subarachnoid haemor- rhage reliably from a traumatic tap. For that purpose, at least 6 and preferably 12 h should have elapsed from symptom onset. In case of subarachnoid haemorrhage sufficient lysis of red cells will have oc- curred in the meantime for bilirubin and oxyhaemoglobin to have formed. These pigments give the cerebrospinal fluid a yellow tinge after centrifugation (xanthochromia); they are invariably detect- able until at least 2 weeks later. The ‘three tube test’

(a decrease in red cells in consecutive tubes in the case of a traumatic puncture) can be helpful, but is unreliable. If the supernatant seems crystal (a) (b) Fig. 24.10.1.7 Aneurysmal subarachnoid haemorrhage in a 31-year- old woman. (a) CT scanning shows evidence of extravasated blood throughout the basal cisterns. (b) CT angiogram, with intravenous contrast, shows an aneurysm at the anterior communicating artery. Box 24.10.1.5 Causes of subarachnoid haemorrhage • Ruptured aneurysm (85%) • Nonaneurysmal perimesencephalic haemorrhage (of venous origin?) (10%) • Rarities (5%) — Arterial dissection (transmural) — Cerebral arteriovenous malformation — Dural arteriovenous fistula — Pituitary apoplexy — Mycotic aneurysm — Cardiac myxoma — Sickle cell disease — Tumours — Spinal arteriovenous malformation or aneurysm — Trauma (without contusion) — Cocaine abuse

 clear, the specimen should be stored in darkness until the absence of blood pigments is confirmed by spectrophotometry. Bilirubin can be formed only in vivo; its demonstration by spectrophotom- etry therefore proves that red blood cells cannot have been intro- duced during the lumbar puncture, whereas oxyhaemoglobin can be formed if a cerebrospinal fluid specimen with red blood cells is left standing before the sample is spun down. Catheter angiog- raphy is rapidly being replaced by CT and MR angiography as a method for demonstrating or excluding an aneurysm as the source of haemorrhage. Treatment of aneurysmal subarachnoid haemorrhage Several complications may occur after a first episode of aneur- ysmal subarachnoid haemorrhage, of which rebleeding and cere- bral ischaemia are the most dreaded. Despite advances in surgical and medical management, the population-based case fatality rate is still around 50%, with half of survivors remaining more or less disabled. As general nursing measures, continuous observation and an intravenous access are essential. A bladder catheter is necessary for monitoring fluid balance. Headache should be relieved in a stepwise approach, with paracetamol and codeine as first steps. Distressing anxiety can be alleviated with short-acting benzodiazepines. Stools should be kept soft with oral laxatives and also by an adequate intake of fluids. Prevention of rebleeding is challenging, if only because any effective measure tends to be offset by an increased risk of is- chaemia. Moreover, at least 10% of all patients with subarach- noid haemorrhage suffer a further bleed within hours of the initial haemorrhage. Over the next 4 weeks the rate of rebleeding without intervention is at least 30%. The immediate case fa- tality of rebleeding is 50%. Endovascular treatment (‘coiling’) is the preferred method to occlude the aneurysm and prevent rebleeding, but not all aneurysms can be treated in this way and surgical treatment by clipping is still necessary for these patients. Antifibrinolytic drugs decrease the rate of rebleeding but do not improve overall outcome. Delayed cerebral ischaemia occurs in up to 25% of patients with a ruptured aneurysm, mainly between day 5 and day 14 after the initial bleed. Understanding of its pathogenesis has been im- peded by simplistic notions about ‘vasospasm’ or ‘clots around vessels’. Narrowing of the arteries at the base of the brain is a factor but not a sufficient one. The total amount of subarachnoid blood is a potent risk factor, but only after rupture of an artery, and the distribution of blood in the subarachnoid space does not predict the site of ischaemia. The calcium antagonist nimodipine, in a dose of 60 mg every 4 h by mouth or nasogastric tube, re- duces the frequency of cerebral ischaemia and poor outcome by about a third; its mode of action is incompletely understood. Hypertension should as a rule be left untreated; it is a compensa- tory reaction to maintain cerebral perfusion. The plasma volume should not be allowed to fall; hyponatraemia is caused by renal sodium depletion and not, as still often believed, by dilution as a result of inappropriate secretion of antidiuretic hormone. Fluids should therefore be replaced and not restricted. The basic intake should be at least 3 litres/day, with intravenous fluids supple- menting oral intake; compensation should be made for fever or a

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